## PEER REVIEW HISTORY



## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | National, clinical cohort study of late effects among survivors of acute lymphoblastic leukemia: the ALL-STAR study protocol. |
| **AUTHORS** | Andres-Jensen, Liv; Skipper, Mette; Mielke Christensen, Kristian; Hedegaard Johnsen, Pia; Aagaard Myhr, Katrine; Kaj Fridh, Martin; Grell, Kathrine; Pedersen, A.; Leisgaard Mørck Rubak, Sune; Ballegaard, Martin; Hørlyck, Arne; Beck Jensen, Rikke; Lambine, Trine-Lise; Gjerum Nielsen, Kim; Tuckuviene, Ruta; Skov Wehner, Peder; Klug Albertsen, Birgitte; Schmiegelow, Kjeld; Frandsen, Thomas Leth |

## VERSION 1 – REVIEW

| | |
|---|---|
| **REVIEWER** | Michael Schündeln<br>Department of Pediatrics III<br>Pediatric Hematology and Oncology<br>University Hospital Essen and the University of Duisburg-Essen<br>Essen<br>Germany |
| **REVIEW RETURNED** | 10-Nov-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Review of “Late effects among survivors of acute lymphoblastic leukemia: the ALL-STAR study protocol.” by Andres-Jensen et al., submitted to BMJ Open as “Study Protocol”.<br><br>Thank you to the Editors for the opportunity to review this well written and thought-provoking manuscript of an important as well as ambitious study.<br><br>As a large majority of patients with acute lymphoblastic leukemia survive, the authors identify the late effects of ALL and its treatment as one of the major challenges for this disease. They propose to establish a cohort of 475 survivors who had been treated from 2008-2018 in the Nordic ALL protocol. The primary endpoints are the cumulative incidence /burden of a number of defined health conditions. Secondary endpoints are functional outcomes of a number of organs. The study aims to correlate the outcomes with a number of possible risk factors.<br><br>The study with its´ comprehensive approach is an addition to a number of ongoing survivorship studies and will augment a number of single center studies on the same subject.<br><br>This manuscript describes a very ambitious ongoing study. Any revision of the study protocol based on my review will not be necessary. However, I believe, this manuscript would benefit from addressing and clarifying some of the points in the REMARKS section in more detail. |

| | |
|---|---|
| | STRENGHTHS of the Manuscript:<br>- Manuscript/ Protocol well written and structured. Well understandable<br>- Statistics: Sample size calculation for the primary study question clearly elaborated and rationale (conservative estimation) of prevalence difference between two groups well explained<br>- Supplemental Reporting accurate: STROBE Criteria point by point elaborated!<br>- Figure 1: informative scheme of the study<br><br>STRENGHTHS of the study:<br>- A Large Cohort including the whole Danish population, treated homogenously by the NOPHO ALL2008 protocol.<br>- A more or less complete register of the Danish ALL cohort is particularly interesting, as the Danish population is also well registered regarding health and socioeconomic information.<br>- A large number of organ systems is being evaluated<br>- Approach to measure cumulative burden instead of only incidence more accurately describing the overall morbidity<br>- Matched controls<br>- A somewhat augmented catalogue of health conditions addressed (e.g. oral conditions)<br>- Well structured, thorough and extensive examination program including physical, laboratory and a number of instrumental examinations. Although very ambitious. Patient flow has to be very well managed!<br>- Genotyping for GWAS for >> 70% of patients (possibly 100% of participants)<br><br>REMARKS to consider / to comment:<br>- The dates of the study should be included in the manuscript. Please include the anticipated timeline.<br>- Why has the study not been set up prospectively to begin with? – Clarify how the infrastructure can be used longitudinally as a “life-long follow-up” platform for this cohort. This would be very important to ensure!<br>- Recruitment of controls: I did not understand, why not siblings are used for controls (like in other studies)? To appoint controls from peers by the survivors is an interesting approach, but may it not also lead to bias? Possibly even more than siblings? Would you be able to clarify or give an example of a comparable study design?<br>- Ethics: I am surprised that information material is not provided for survivors < 15 but only parents. I believe ethically (and from a standpoint of adherence) younger participants should also be addressed directly. Possibly this is a misunderstanding for my part. Would you be able to clarify?<br>- Ethics: Language of tests, population heterogeneity. Are all the questionnaires and study information material in Danish language? Would this lead to exclusion of certain survivor-subgroups? Or is it not necessary to include different languages due to the previously described homogeneity in the danish population?<br>- You omit the question of fertility/ semen work up/ ovarian function etc. from the study. Why not add this question - as secondary question. I don’t believe that is would necessarily decrease the participant number overall.<br><br>MINOR REMARKS: |

| | |
|---|---|
| | The remark that the “Nordic countries differ from other western countries by complete … access to healthcare... “ (p22 l 44. ). Is a somewhat misleading and appears a little unjust to most of the EU countries I am aware of. |

| | |
|---|---|
| **REVIEWER** | Jennifer McNeer<br>University of Chicago, USA |
| **REVIEW RETURNED** | 04-Dec-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | This is a very clear description of a protocol to comprehensively assess long-term and late effects in survivors of ALL, all treated on a single clinical trial (NOPHO ALL2008). There is a very well-defined approach in terms of eligible patients and controls, as well as a detailed description of the assessments that are to be carried out. This study will be important to characterize the health of ALL survivors compared to controls, and will be excellent as a comparison to outcomes reported by other similar studies (SJCRH CCSS for example) conducted within very different healthcare systems.<br><br>I have a few comments for clarification:<br>-Near the end of the introduction, it is stated that no prior studies included Nordic survivors, but one of the referenced studies is a Nordic study. Is it that there were no Danish survivors included in other cohorts?<br>-In several places (Questionnaire Data under Data Collection, for example), the term "familiar dispositions". Should it be "familial" instead?<br>-For pancreatic function, why will fecal elastase-1 only be evaluated in survivors?<br>-In the description of the approach to bone mineral density, the use of unpublished USA and German reference material is alluded to. Is it possible to clarify what the normal ranges/standard deviations will be rather than only stating unpublished material will be used?<br>-In the section on neuropathy there are two typos. ALL-STAR "controls" should be "control", and "21-minutes Holter" should be "21-minute Holter"<br>-In the section on pubertal status, again the term "unpublished" reference is used and could perhaps be clarified.<br>-Supplementary Table 2: in the notes section at the bottom, I believe the 5 should be a 4, as it seems to refer to Psychosocial instruments and Cognitive in the table.<br>-Supplementary Table 3: there appear to be a few typos. For consistency, 8-00 should be 8.00, and 1530 should be 15.30 |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Michael Schündeln
Institution and Country
Department of Pediatrics III
Pediatric Hematology and Oncology
University Hospital Essen and the University of Duisburg-Essen
Essen

Germany

Reviewer: 2
Reviewer Name
Jennifer McNeer
Institution and Country
University of Chicago, USA

Reviewer: 1

Comments to the Author
Review of “Late effects among survivors of acute lymphoblastic leukemia: the ALL-STAR study protocol.” by Andres-Jensen et al., submitted to BMJ Open as “Study Protocol”.

Thank you to the Editors for the opportunity to review this well written and thought-provoking manuscript of an important as well as ambitious study.

As a large majority of patients with acute lymphoblastic leukemia survive, the authors identify the late effects of ALL and its treatment as one of the major challenges for this disease. They propose to establish a cohort of 475 survivors who had been treated from 2008-2018 in the Nordic ALL protocol. The primary endpoints are the cumulative incidence /burden of a number of defined health conditions. Secondary endpoints are functional outcomes of a number of organs. The study aims to correlate the outcomes with a number of possible risk factors.

The study with its´ comprehensive approach is an addition to a number of ongoing survivorship studies and will augment a number of single center studies on the same subject.

This manuscript describes a very ambitious ongoing study. Any revision of the study protocol based on my review will not be necessary. However, I believe, this manuscript would benefit from addressing and clarifying some of the points in the REMARKS section in more detail.

STRENGHTHS of the Manuscript:
- Manuscript/ Protocol well written and structured. Well understandable
- Statistics: Sample size calculation for the primary study question clearly elaborated and rationale (conservative estimation) of prevalence difference between two groups well explained
- Supplemental Reporting accurate: STROBE Criteria point by point elaborated!
- Figure 1: informative scheme of the study

STRENGHTHS of the study:
- A Large Cohort including the whole Danish population, treated homogenously by the NOPHO ALL2008 protocol.
- A more or less complete register of the Danish ALL cohort is particularly interesting, as the Danish population is also well registered regarding health and socioeconomic information.
- A large number of organ systems is being evaluated
- Approach to measure cumulative burden instead of only incidence more accurately describing the overall morbidity
- Matched controls
- A somewhat augmented catalogue of health conditions addressed (e.g. oral conditions)
- Well structured, thorough and extensive examination program including physical, laboratory and a number of instrumental examinations. Although very ambitious. Patient flow has to be very well managed!
- Genotyping for GWAS for >> 70% of patients (possibly 100% of participants)

REMARKS to consider / to comment:
- The dates of the study should be included in the manuscript. Please include the anticipated timeline.

**VERSION 2 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Michael Schündeln<br>Pediatric Hematology and Oncology,<br>Department of Pediatrics III,<br>University Hospital Essen and the University of Duisburg-Essen, Essen,<br>Germany. |
| **REVIEW RETURNED** | 17-Dec-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you very much for giving me the opportunity to review the new version of the manuscript. The authors have addressed all of my questions and comments.<br>I believe the manuscript may be published as is.<br>I wish the authors good luck with their well designed and important study! |

| | |
|---|---|
| **REVIEWER** | Jennifer McNeer<br>University of Chicago<br>USA |
| **REVIEW RETURNED** | 19-Dec-2020 |

| | |
|---|---|
| **GENERAL COMMENTS** | The authors have thoughtfully addressed the comments and questions from the first reviews. The manuscript has been edited accordingly. |